Zoledronic Acid and Survival in Patients with Metastatic Bone Disease from Lung Cancer and Elevated Markers of Osteoclast Activity

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Introduction: Bone metastases from non-small cell lung cancer (NSCLC) are associated with skeletal-related events (SREs) and elevated levels of N-telopeptide of type I collagen (NTX) in some patients. Zoledronic acid (ZOL) reduces SRE risk and NTX levels.
Methods: To assess effects of baseline variables, including NTX levels (normal = NTX $<$ 64 nmol/mmol creatinine; high = NTX $\geq$ 64 nmol/mmol creatinine), on treatment effects in NSCLC patients, a retrospective analysis was performed in NSCLC patients with bone metastases (N = 382) treated with ZOL or placebo every 3 weeks in a 21-month randomized clinical trial in patients with NSCLC or other solid tumors. Cox proportional hazards models assessed relative risks (RRs) of SREs, bone lesion progression, and death. Multivariate models analyzed covariate effects on survival.
Results: For both placebo- and ZOL-treated patients, high baseline NTX correlated with increased SRE risk (p = 0.068 and 0.012, respectively). Although high versus normal baseline NTX correlated with more than twofold increased risks of bone lesion progression and death in the placebo group (p = 0.039 and 0.001, respectively), correlations were weaker in the ZOL group (RR = 1.38; p = 0.0186 and RR = 1.27; p = 0.142, respectively), suggesting an interaction effect of ZOL and baseline NTX. Among patients with high baseline NTX, ZOL significantly reduced the RR of death by 35% versus placebo (p = 0.024). Per multivariate analysis, ZOL treatment (p = 0.005), higher lymphocyte count (p = 0.011), performance status 0 to 1 (p = 0.012), and absence of narcotic use (p = 0.016) correlated with improved survival.
Conclusions: This retrospective analysis revealed statistically significant correlations between ZOL and increased survival versus placebo in NSCLC patients and high baseline NTX levels.

Key Words: Bone markers, Non-small cell lung cancer, N-telopeptide of type I collagen, Survival, Zoledronic acid.

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Lung cancer is the most common cancer worldwide,[1] and non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer.[2,3] Advanced NSCLC is often highly symptomatic,[4] and an estimated 30 to 40% of patients develop bone metastases.[5] In these patients, skeletal complications can cause considerable morbidity and may result in functional impairment and loss of mobility. Increased tumor growth in bone can result in increased tumor growth leading to potentially debilitating skeletal-related events (SREs) such as pathologic fractures and bone pain requiring palliative radiotherapy. These SREs are clinically meaningful sequelae that are associated with increased health care costs and decreased quality of life.[6–8] Moreover, pathologic fractures have been associated with a significantly increased risk of death in patients with malignant bone disease from multiple myeloma or bone metastases from breast cancer or prostate cancer.[9,10] Although no significant correlation was observed in patients with lung cancer or other aggressive solid tumors because of their short median time of survival in patients enrolled in the trial, the extended survival of patients in this setting with advances in primary therapies may increase the risk of death in patients who experience a pathologic fracture. Therefore, preventing SREs or delaying their onset might not only improve quality of life but also potentially extend survival.

Interactions between tumor and bone typically result in increased rates of bone metabolism, which can be detected by increases in levels of biochemical markers of bone metabolism.[11,12] For example, serum bone-specific alkaline phosphatase (BALP) levels reflect ongoing levels of bone formation, and N-telopeptide of type I collagen (NTX) is a sensitive marker of osteolysis.[11,12] Bone markers provide insight into the extent or aggressiveness of bone metastases.[11,13] In an

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exploratory analysis of the placebo-control arms of two phase III trials of zoledronic acid, cancer patients with bone metastases and elevated NTX levels (≥ 50 nmol/mmol creatinine) were found to have approximately twofold increases in their risk of SREs and bone disease progression and an approximately three- to fivefold increased risk of death compared with patients with low NTX levels ($p < 0.01$ for all).[11] Similarly, compared with patients with low BALP levels, patients with elevated BALP levels on study had significant increases in their relative risks (RRs) of SREs and death. Recent bone marker assessment results during bisphosphonate treatment have also been shown to have prognostic significance.[12]

Bisphosphonates are inhibitors of bone resorption used in the oncology setting for the prevention of SREs and treatment of hypercalcemia of malignancy in patients with bone metastases. Zoledronic acid (ZOMETA; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland) is the only bisphosphonate that has demonstrated efficacy for the prevention of SREs in patients with bone metastases from a wide range of solid tumors including breast cancer, prostate cancer, and lung cancer.[14–17] In a phase III, multicenter, randomized, placebo-controlled trial, zoledronic acid (4 mg via 15-minute infusion every 3 weeks for up to 21 months) significantly delayed the onset and reduced the ongoing risk of SREs compared with placebo in patients with bone metastases secondary to lung cancer and other aggressive solid tumors.[15,16] Zoledronic acid also significantly lowered NTX levels relative to baseline.[12,16] Approximately one half of the enrolled patients had NSCLC, and their 1-year survival rate was approximately 30%.[15] However, correlations between baseline NTX levels and outcomes have not been evaluated specifically in patients with NSCLC using the currently accepted upper limit of normal for NTX levels in oncology patients (i.e., 64 nmol/mmol creatinine), and prognostic models for survival in patients with bone metastases from NSCLC are needed. Moreover, although survival was not a primary end point of this zoledronic acid study, survival was approximately 1 month longer for zoledronic acid-treated patients with NSCLC compared with placebo (not statistically significant).[15]

The current analysis was initiated to investigate whether baseline bone marker levels had prognostic significance in patients with NSCLC treated with zoledronic acid in a phase III, randomized, placebo-controlled trial and whether the nonsignificant survival increase with zoledronic acid versus placebo in the overall NSCLC stratum was driven by subsets of patients who may have benefited more than others during treatment.[15,16]

PATIENTS AND METHODS

This was a retrospective analysis of patients with NSCLC in a phase III, multicenter, randomized, placebo-controlled trial of zoledronic acid in patients with bone metastases from NSCLC or other solid tumors (not including breast or prostate cancer).[15,16] Details of the study design have been previously published.[15,16] A brief description is provided herein.

Patients and Treatment

Patients with documented bone metastases secondary to NSCLC or other solid tumors (excluding breast or prostate cancer) were eligible for this trial. Baseline disease characteristics, radiologic examinations, Eastern Cooperative Oncology Group (ECOG) performance status, and serum and urine chemistry values were assessed before the initiation of treatment. Patients were randomized to receive zoledronic acid (4 mg or 8 mg) or placebo via 15-minute infusion every 3 weeks for 9 months. Patients who completed this core phase were offered to continue blinded treatment for another year. The final analysis was performed at 21 months. After the study was initiated, the 8-mg zoledronic acid dose was reduced to 4 mg to ensure renal safety, and this group was thereafter referred to as the zoledronic acid 8/4-mg group. The majority of infusions in this group were administered at the 4-mg dose level, and outcomes were similar between the 4-mg and the 8/4-mg treatment arms. Therefore, both zoledronic acid groups are combined in the current analysis. Previous analyses have been performed based on the combined groups.[12]

Patients with NSCLC who were treated with either zoledronic acid or placebo were included in the retrospective analysis and were also analyzed according to baseline NTX levels.

Clinical Endpoints

In the prospective trial, the proportion of patients with an SRE was the primary end point.[15,16] The SRE composite end point is an objective measurement of clinically meaningful skeletal morbidity.[18] Survival is the primary outcome evaluated in the current analyses because this is the ultimate end point in oncology trials and is not affected by observation bias. Bone lesion progression was also evaluated because it is a variable that has been correlated with bone marker level increases,[19] although this end point was limited by the frequency of radiologic assessment in the current database (approximately every 3 months during the trial).[15,16]

Bone Markers

Baseline urinary NTX levels were assessed only in patients treated in the United States or Canada. Urinary NTX was measured by enzyme-linked immunosorbent assay, normalized to urinary creatinine, and categorized according to the following variables: low NTX, < 64 nmol/mmol creatinine; high NTX, ≥ 64 nmol/mmol creatinine, based on the upper limit of normal for disease-free premenopausal women. Serum BALP levels were also measured by enzyme-linked immunosorbent assay.

Statistical Analyses

Patients with NSCLC who had baseline NTX and BALP assessments were included in the bone marker subset analyses. Cox regression models were used to assess associations between bone marker levels and outcomes (e.g., SREs, bone lesion progression, and death) and between bisphosphonate treatment and survival in patients with normal or high NTX.[20] Kaplan-Meier estimates were computed for the proportion of patients alive over time by group.[21] The cumulative

probability of an on-study SRE was assessed using survival-adjusted cumulative incidence functions because of the competing risk of death. After the significant benefit of zoledronic acid in the high NTX subset was identified, a series of multivariate analyses to further investigate the effect were preplanned and then executed.

Multivariate regression analyses were performed to investigate the potential effects of baseline characteristics and treatment effects on survival. For parameters without an established cut-off value (e.g., the upper limit of normal), either the median for the specific population in the model was used or the parameter was treated as a continuous variable. The baseline variables included in each of these models were treatment group (zoledronic acid 4 mg or 8/4 mg versus placebo); sex; race; cancer duration; age at study entry; weight at study entry; Functional Assessment of Cancer Therapy-General (FACT-G) total score; Brief Pain Inventory (BPI) composite pain score; SRE history (yes/no); analgesic usage (none or minor analgesics or coanalgesics versus narcotics); ECOG performance status score; predominant lesion type; NTX status (normal or high); BALP status (normal or $\geq$ 146 U/L); and the following variables using the median (listed in parentheses for the high-NTX subset) as a cut-off value: urinary NTX level (102 nmol/mmol creatinine), serum creatinine (1 mg/dL), serum lactate dehydrogenase ([LDH] 246.5 U/L), lymphocytes (14.025%; and as a continuous variable), albumin (38 g/L; and as a continuous variable), and hemoglobin (11.7 g/dL; and as a continuous variable). All available baseline demographic and disease characteristics data were included in the univariate and full multivariate models to ensure that variables of unexpected significance were captured in the reduced model. For generation of the reduced model, the initial full model included only patients for whom there was a complete data set for all variables to minimize the confounding effect of correlated variables on the model. The majority of patients who were not included in this model were missing either NTX or BPI data.

To identify any significant interactions between treatment and each baseline variable, multivariate models were generated using the treatment group, the respective baseline prognostic variable, and their interaction term. The multivariate model included all baseline variables, and a reduced model was generated by backward elimination until only significant variables remained in the model; variables were considered significant if $p < 0.05$.

RESULTS

Baseline Characteristics for Patients with NSCLC

In the phase III trial of zoledronic acid in patients with lung cancer or other solid tumors, 382 patients with NSCLC were randomized to zoledronic acid ($n = 259$) or placebo ($n = 123$) (Table 1).[15,16] Patient demographics and baseline disease characteristics were similar between the treatment groups. A total of 263 patients had baseline NTX assessments, and 144 (55%) had high baseline NTX levels. This subset had a lower median time from the diagnosis of bone metastases to study entry compared with the overall population.

TABLE 1. Patient Demographics and Baseline Disease Characteristics (Study 011)

	NSCLC Patients ($n = 382$)		High-NTX Subset ($n = 144$)	
Factor	**Zoledronic Acid ($n = 259$)**	**Placebo ($n = 123$)**	**Zoledronic Acid ($n = 102$)**	**Placebo ($n = 42$)**
Median age, yr (range)	63 (37–88)	63 (39–82)	64 (37–88)	64 (43–82)
Sex, *n* (%)				
Male	178 (68.7)	78 (63.4)	68 (66.7)	26 (61.9)
Female	81 (31.3)	45 (36.6)	34 (33.3)	16 (38.1)
Race, *n* (%)				
White	230 (88.8)	112 (91.1)	88 (86.3)	36 (85.7)
Black/Asian/Other	29 (11.2)	11 (8.9)	14 (13.7)	6 (14.3)
ECOG PS 0 or 1, *n* (%)	214 (82.6)	110 (89.4)	86 (84.3)	36 (85.7)
BPI < 3.25 U, *n* (%)[a]	104 (43.9)	52 (47.7)	40 (40.0)	15 (37.5)
SGOT < 23.0 U, *n* (%)[a]	129 (50.0)	55 (45.8)	46 (45.1)	17 (40.5)
Previous SRE, *n* (%)[a]	174 (67.4)	91 (75.2)	73 (72.3)	35 (83.3)
NTX level, nmol/mmol creatinine[b]	84.8 ± 68.5	77.8 ± 45.2	119.14 ± 75.1	107.88 ± 41.9
Serum creatinine, mg/dL[b]	1.01 ± 0.25	1.01 ± 0.21	0.97 ± 0.21	0.95 ± 0.22
Baseline LDH < 246.5 U/L, *n* (%)[a]	128 (49.6)	61 (50.8)	63 (61.8)	26 (61.9)
Baseline lymphocytes < 14.025, *n* (%)[a]	126 (49.4)	61 (51.3)	60 (58.8)	25 (59.5)
Median time since diagnosis of bone metastases, months	0.82	0.61	0.36	0.43

Data from the trials by Rosen et al.[15,16]

[a] Percentages were calculated using only those patients who had data for this parameter.

[b] Values reported as mean ± standard deviation.

NSCLC, non-small cell lung cancer; NTX, N-telopeptide of type I collagen; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BPI, Brief Pain Inventory; U, unit; SGOT, serum glutamic-oxaloacetic transaminase; SRE, skeletal-related event; LDH, lactate dehydrogenase.

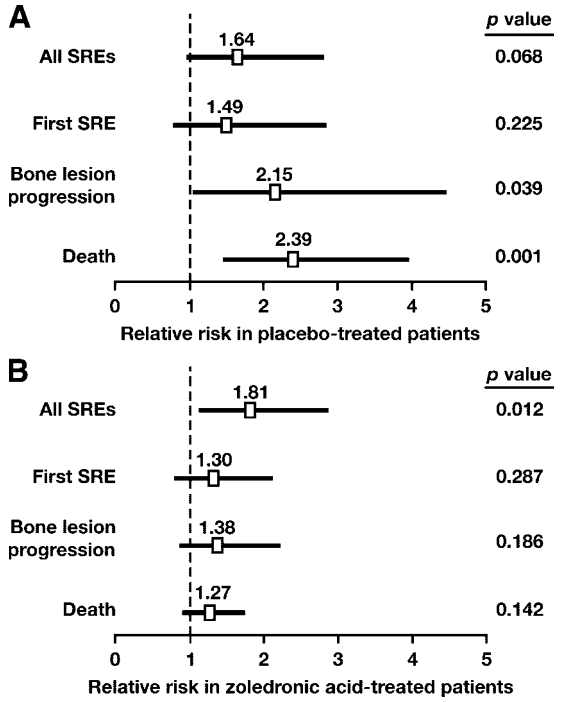

FIGURE 1. Relative risk of on-study skeletal complications, disease progression, or death for patients with non-small cell lung cancer and high N-telopeptide of type 1 collagen (NTX) levels (defined as ≥ 64 nmol/mmol creatinine) versus low NTX levels (< 64 nmol/mmol creatinine) treated with (*A*) placebo or (*B*) zoledronic acid (4 mg + 8/4 mg), by univariate analysis. Length of horizontal line represents the 95% confidence interval. SRE, skeletal-related event.

Baseline NTX Levels and Risks of Clinical Events

Among 80 patients in the placebo group who had baseline NTX assessments, 42 (53%) had high levels. High NTX was associated with a nonsignificant increased risk of SREs (RR = 1.64; $p = 0.068$) and a first SRE (RR = 1.49; $p = 0.225$) compared with normal baseline NTX (Fig. 1*A*). Patients with high baseline NTX levels were at a significantly increased risk of bone lesion progression (RR = 2.15; $p = 0.039$) and death (RR = 2.39; $p = 0.001$) compared with the subset of placebo-group patients who had normal baseline NTX levels.

Among the 183 zoledronic acid-treated patients with baseline NTX assessments, 102 (56%) had high levels. In the zoledronic acid group, patients with high baseline NTX had a significant 81% increased risk of any SRE (RR = 1.81; $p = 0.012$) and a trend toward an increased risk of a first SRE (RR = 1.30; $p = 0.287$) compared with patients with normal NTX at baseline. In contrast with the results in the single placebo group, high baseline NTX was not associated with significant increases in the risks of bone lesion progression or death among zoledronic acid-treated patients ($p = 0.186$ and 0.142, respectively; Fig. 1*B*), despite the larger sample size that resulted from combining the two treatment groups.

Skeletal Morbidity and Overall Survival

Among all patients with NSCLC, zoledronic acid significantly reduced the risk of a first on-study SRE versus placebo ($p = 0.028$; Fig. 2). Andersen-Gill multiple event analysis, which accounts for all SREs and for the timing of SREs, revealed a significant 38% reduction in the risk of developing SREs for the zoledronic acid groups compared with the placebo group (RR = 0.62; $p \leq 0.001$). There were no significant differences in time to bone lesion progression between groups. Radiologic assessments mandated by the study, however, were only performed approximately every 3 months unless clinically indicated.

Median survival after study entry was 177 days for patients with NSCLC. Patients with NSCLC treated with zoledronic acid lived approximately 1 month longer than those in the placebo group, but this difference was not statistically significant (median survival, 187 days for zoledronic acid versus 157 days for placebo; $p = 0.539$). Based on the observations regarding survival and the weaker prognostic significance of high baseline NTX levels among patients who were treated with zoledronic acid versus placebo, the effects of baseline NTX levels on zoledronic acid treatment benefits were examined.

Analysis by *N*-Telopeptide Level in Patients with NSCLC

Subset analyses were performed on the 262 patients who had baseline NTX assessments. Statistical heterogeneity for the treatment effect of zoledronic acid on survival between the high and low NTX groups was detected ($p = 0.018$), suggesting that these two groups were different and that inferences regarding possible treatment effects should be made separately for them. In the group of 118 patients who had normal baseline NTX levels, the Kaplan-Meier survival curves (Fig. 3*A*) and risk of death were similar for the zoledronic acid-treatment groups compared with placebo (RR = 1.326; $p = 0.223$). In contrast, among the 144 patients with high baseline NTX levels, zoledronic acid and placebo groups had significantly different Kaplan-Meier survival curves (Fig. 3*B*), and zoledronic acid significantly reduced the risk of death by 35% compared with placebo (RR = 0.652; $p = 0.025$). Further assessments were performed on the high-NTX subset to investigate factors that might have contributed to the survival differences between the zoledronic acid and placebo groups.

In the high-NTX subgroup, the majority of patients (85%) in both the treatment and placebo groups had an ECOG performance status of 0 or 1, approximately one half of the patients were ≥ 65 years of age, and characteristics were well balanced between the treatment groups (Table 1).[15,16] Moreover, the percentage of patients receiving concomitant chemotherapy was similar between patients who had high NTX levels and the overall patient population in each treatment group. Approximately 80% of all patients receiving zoledronic acid and patients with elevated NTX levels receiving zoledronic acid also received chemotherapy. Similarly, 76% of all placebo-treated patients and placebo-treated patients with elevated NTX levels were receiving chemotherapy.

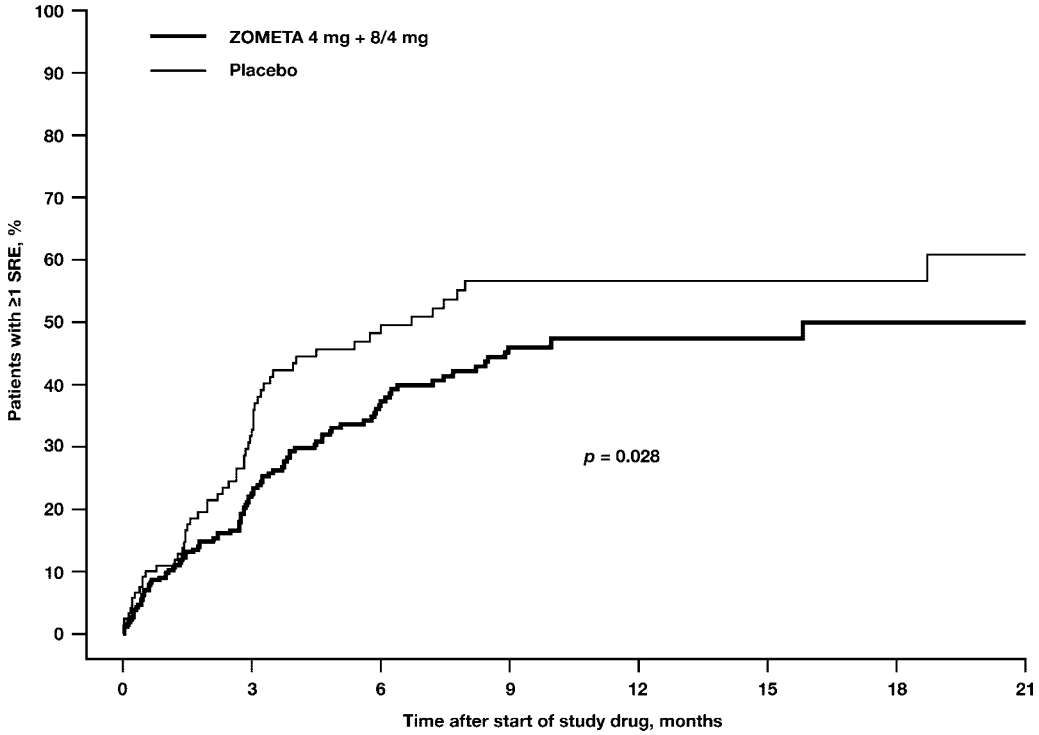

FIGURE 2. Proportion of patients with non-small cell lung cancer who experienced ≥ 1 on-study skeletal-related event (SRE).

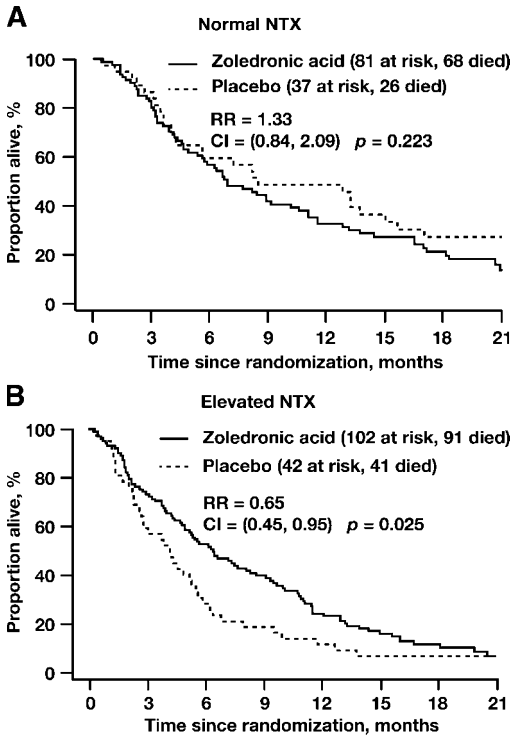

FIGURE 3. Survival patterns of patients with non-small cell lung cancer, based on N-telopeptide of type 1 collagen (NTX) levels at baseline. *A* Kaplan-Meier survival curves for patients with normal baseline NTX. *B* Kaplan-Meier survival curves for patients with elevated baseline NTX. RR, relative risk; CI, confidence interval.

Analysis of Baseline Covariates and Treatment Effects on Survival (Overall)

For the overall population of patients with NSCLC and bone marker assessments, 12 baseline variables were found to significantly correlate with improved survival in univariate models: high FACT-G total score; lower BPI composite pain score; female sex; no baseline requirement for narcotic pain medication; ECOG performance status of 0 or 1; normal NTX status; normal BALP status; serum creatinine < 1.0 mg/dL; absolute lymphocyte count; and serum glutamic-oxaloacetic transaminase, albumin, and LDH below the median value. However, after adjustment in a multivariate model, NTX and BALP status and levels of creatinine, serum glutamic-oxaloacetic transaminase, and lymphocytes decreased in prognostic significance, and treatment with zoledronic acid showed a trend toward a survival benefit compared with placebo (RR = 0.765; $p = 0.103$).

The effects of baseline covariates on the association between treatment groups and survival were assessed in two multivariate models (Table 2). The first of these included all patients with information for each of the respective baseline variables (the number of patients contributing to these analyses differs depending on variable), and the second included only patients with a complete set of data for every variable ($n = 244$). In both models, survival benefits with zoledronic acid treatment significantly varied by race, ECOG performance status, and baseline NTX level variables. In the second analysis, baseline LDH status emerged as a covariable that profoundly affected the survival benefit. In a reduced multivariate model involving patients with complete data ($n = 244$), adjusting for the effects of FACT-G total score, nar-

TABLE 2. Multivariate Model with Treatment Effect, Baseline Prognostic Variable, and Their Interaction Term

		Patients with Respective Variable					Patients with All Variables (n = 244)				
Covariate[a]	**Domain**	***n***	**RR**	**95% CI**	***p***	***p*[b]**	***n***	**RR**	**95% CI**	***p***	***p*[b]**
BPI score	<3.25 units	156	1.159	(0.797–1.686)	0.441	0.065	108	1.084	(0.684–1.719)	0.732	0.371
	≥3.25 units	190	0.726	(0.525–1.004)	0.053		136	0.823	(0.558–1.215)	0.327	
Race	White	342	1.001	(0.784–1.279)	0.993	0.018	216	1.043	(0.761–1.428)	0.794	0.011
	Black/Asian/Other	40	0.391	(0.187–0.818)	0.013		28	0.291	(0.115–0.733)	0.009	
ECOG PS	Active	324	0.947	(0.737–1.217)	0.670	0.048	213	0.990	(0.719–1.362)	0.950	0.039
	Some impairment	57	0.477	(0.254–0.898)	0.022		31	0.391	(0.172–0.890)	0.025	
NTX status	<64.0	118	1.340	(0.852–2.106)	0.205	0.020	109	1.344	(0.838–2.154)	0.220	0.024
	≥64.0	145	0.672	(0.465–0.971)	0.034		135	0.667	(0.454–0.979)	0.039	
Serum LDH	<246.5	189	1.119	(0.799–1.566)	0.513	0.136	169	1.241	(0.863–1.785)	0.245	<0.001
	≥246.5	189	0.783	(0.566–1.084)	0.141		75	0.342	(0.201–0.583)	<0.001	
Lymphocytes	<14.025%	187	0.896	(0.648–1.239)	0.507	0.677	131	0.620	(0.417–0.923)	0.019	0.026
	≥14.025%	187	0.991	(0.704–1.394)	0.957		113	1.231	(0.783–1.936)	0.368	
SGOT	<23.0	184	1.044	(0.737–1.479)	0.808	0.468	109	1.266	(0.788–2.034)	0.330	0.119
	≥23.0	194	0.877	(0.639–1.204)	0.417		135	0.780	(0.531–1.144)	0.203	
Albumin	<38	180	0.779	(0.570–1.120)	0.193	0.279	102	0.649	(0.406–1.038)	0.071	0.104
	≥38	197	1.035	(0.749–1.432)	0.834		142	1.075	(0.731–1.581)	0.713	

[a] The following covariates showed no trends for treatment by covariate interactions in either model ($p > 0.15$): Cancer duration ≥5 vs. <5 mo; age ≥63 vs. <63 yr; weight ≥71 vs. <71 kg; Functional Assessment of Cancer Therapy-General total score ≥70 vs. <70; sex; narcotics use; lesion type; prior skeletal-related event; bone-specific alkaline phosphatase ≥64 vs. <64 U/L; serum creatinine <1 vs. ≥1 mg/dL.

[b] Test of treatment by covariate interaction.

RR, relative risk; CI, confidence interval; BPI, Brief Pain Inventory composite score; ECOG, Eastern Cooperative Oncology Group; PS, performance status score; NTX, urinary N-telopeptide of type I collagen in nmol/mmol creatinine; LDH, lactate dehydrogenase, in g/L; SGOT, serum glutamic-oxaloacetic transaminase; Albumin, in g/L.

cotics use, ECOG performance status, SRE history, baseline lymphocyte, and baseline albumin levels, baseline LDH level significantly influenced the survival effect of zoledronic acid ($p = 0.005$ for LDH above versus below the median value [e.g., the test of treatment benefit by covariate interaction]). Zoledronic acid produced an approximately 2.4-fold decrease in risk of death versus placebo in patients with elevated LDH ($p = 0.0015$), and a nonsignificant 4.3% increase in the low LDH patients ($p = 0.823$). In the reduced multivariate model investigating the effects of LDH level on treatment benefits, only FACT-G score, narcotics use, ECOG performance status, prior SRE, baseline lymphocyte, and albumin levels were significant covariates for a survival effect of zoledronic acid, whereas NTX was not a significant covariate.

Analysis of Baseline Covariates and Treatment Effects on Survival (High NTX)

In univariate models in the high-NTX subset, the following covariates significantly correlated with improved survival: treatment with zoledronic acid versus placebo, higher FACT-G total score, no baseline requirement for narcotic pain medication, ECOG performance status of 0 or 1, and higher than the median lymphocyte level (Table 3). However, after adjustment in a multivariate model, only treatment with zoledronic acid versus placebo, higher FACT-G total score, and no requirement for narcotic pain medication remained significant. The reduced multivariate model showed that zoledronic acid was associated with a statistically significant 43% reduction in the risk of death compared with placebo (RR = 0.565; $p = 0.0047$). Therefore, this multivariate model confirmed the survival benefit for zoledronic acid versus placebo that was observed in the initial analyses in the high-NTX subset.

Similar to the analyses performed in the overall population of patients with NSCLC, the effects of baseline covariates on the survival benefit of zoledronic acid were analyzed in two multivariate models in the high baseline-NTX subset (Table 4). In both models, survival effects from treatment were found to vary significantly based on age, race, serum LDH level, and NTX level relative to the median for the high-NTX group (102.0 nmol/mmol creatinine). The survival benefit in patients treated with zoledronic acid was greatest among patients with a shorter time since their primary cancer diagnosis, younger age, and less profound NTX elevations.

The current analysis was designed to investigate differences in treatment effects based on patients' bone marker levels; however, other significant covariates for treatment effects were identified, including race, performance status, and LDH level. Further analyses are underway to investigate how the significant covariates associated with improved survival with zoledronic acid treatment versus placebo interact, especially in regard to LDH status.

DISCUSSION

Zoledronic acid is the only bisphosphonate to be appropriately evaluated in the treatment of both osteolytic and osteoblastic bone metastases secondary to a broad range of tumors, including NSCLC, and has been shown to significantly reduce the incidence and rate of skeletal complications.[15,16] In addition to prevention of SREs and palliative effects on bone pain,[22–24] the analyses presented herein sug-

TABLE 3. Cox Regression Analysis of Correlations Between Baseline Variables and Treatment and Survival Outcomes (High NTX Population)

	Univariate			Reduced Multivariate		
Covariate	**RR**	**95% CI**	***p***	**RR**	**95% CI**	***p***
Treatment, ZOL vs. PLA	0.657	(0.447–0.967)	0.033	0.565	(0.381–0.840)	0.005
Cancer duration, per 1-yr ↑	1.039	(0.956–1.129)	0.370			
Age, per 1-yr ↑	1.008	(0.990–1.026)	0.406			
FACT-G score, per 1-unit ↑	0.985	(0.973–0.996)	0.008			
BPI score, per 1-unit ↑	1.066	(0.983–1.156)	0.123			
Race, Black/Asian/Other vs. White	0.635	(0.374–1.077)	0.092			
Mild/Strong narcotics vs none	1.797	(1.144–2.823)	0.011	1.757	(1.110–2.780)	0.016
ECOG PS: 2 vs. 0 or 1	1.971	(1.186–3.276)	0.009	1.941	(1.158–3.255)	0.012
Prior SRE	1.174	(0.778–1.772)	0.444			
NTX ≥ 64.0	1.263	(0.885–1.801)	0.198			
BALP ≥ 146.0	1.004	(0.688–1.465)	0.983			
Lymphocytes, per 1% ↑	0.974	(0.957–0.992)	0.004	0.977	(0.960–0.995)	0.011
LDH ≥ 246.5	1.199	(0.830–1.732)	0.334			
Albumin, per 1-unit ↑	0.957	(0.913–1.003)	0.065			

RR, relative risk; CI, confidence interval; ZOL, zoledronic acid; PLA, placebo; ↑, increase; FACT-G, Functional Assessment of Cancer Therapy-General total score; BPI, Brief Pain Inventory composite score; vs, versus; ECOG, Eastern Cooperative Oncology Group; PS, performance status score; SRE, skeletal-related event; NTX, urinary N-telopeptide of type I collagen, in nmol/mmol creatinine; BALP, bone-specific alkaline phosphatase, in U/L; LDH, lactate dehydrogenase, in g/L; albumin, in g/L.

TABLE 4. Multivariate Model with Treatment Effect, Baseline Prognostic Variable, and Their Interaction Term (High NTX Population)

		Patients with Respective Variable					Patients with All Variables (n = 135)				
Covariate[a]	**Domain**	***n***	**RR**	**95% CI**	***p***	***p*[b]**	***n***	**RR**	**95% CI**	***p***	***p*[b]**
Cancer duration	<5.02 mo	77	0.462	(0.273–0.784)	0.004	0.107	70	0.438	(0.252–0.763)	0.004	0.078
	≥5.02 mo	67	0.853	(0.502–1.449)	0.557		65	0.878	(0.511–1.509)	0.639	
Age	<63 yr	63	0.403	(0.221–0.732)	0.003	0.043	58	0.386	(0.208–0.718)	0.003	0.035
	≥63 yr	81	0.886	(0.550–1.429)	0.621		77	0.904	(0.551–1.482)	0.689	
Race	White	124	0.791	(0.528–1.183)	0.254	0.014	116	0.803	(0.530–1.218)	0.302	0.009
	Other	20	0.201	(0.073–0.552)	0.002		19	0.173	(0.059–0.505)	0.001	
Narcotics used	None	29	1.115	(0.462–2.694)	0.809	0.120	29	1.115	(0.461–2.693)	0.809	0.113
	Mild/strong	114	0.514	(0.338–0.781)	0.002		106	0.502	(0.325–0.778)	0.002	
NTX	<102.0	71	0.964	(0.577–1.609)	0.887	0.001	68	0.950	(0.562–1.605)	0.847	0.002
	≥102.0	73	0.270	(0.152–0.479)	<0.001		67	0.263	(0.144–0.482)	<0.001	
BALP	<146.0	47	0.988	(0.495–1.971)	0.972	0.146	44	1.040	(0.505–2.139)	0.916	0.123
	≥146.0	97	0.537	(0.344–0.839)	0.006		91	0.530	(0.335–0.840)	0.007	
LDH	<246.5	89	0.843	(0.526–1.351)	0.478	0.030	84	0.883	(0.537–1.450)	0.622	0.022
	≥246.5	55	0.356	(0.191–0.661)	0.001		51	0.345	(0.183–0.650)	0.001	
Hemoglobin	<11.70	77	0.454	(0.269–0.767)	0.003	0.075	73	0.476	(0.278–0.815)	0.007	0.121
	≥11.70	67	0.892	(0.525–1.515)	0.672		62	0.876	(0.503–1.528)	0.641	

[a] The following covariates showed no trends for treatment by covariate interactions in either model ($p > 0.15$): Functional Assessment of Cancer Therapy-General total score ≥70 vs. <70; Brief Pain Inventory composite score ≥3.25 vs. <3.25; sex; Eastern Cooperative Oncology Group performance status score active vs. some impairment; prior skeletal-related event; lesion type; creatinine <1 vs. ≥1 mg/dL; lymphocytes ≥14.025% vs. <14.025%; serum glutamic-oxaloacetic transaminase <23 vs. ≥23 U/L; serum albumin <38 g/L vs. ≥38 g/L.

[b] Test of treatment by covariate interaction.

NTX, urinary N-telopeptide of type I collagen, in nmol/mmol creatinine; RR, relative risk; CI, confidence interval; BALP, bone-specific alkaline phosphatase, in U/L; LDH, lactate dehydrogenase, in g/L.

gest that zoledronic acid may offer additional benefits in NSCLC patients who have high NTX levels at baseline.

In the current analysis, zoledronic acid treatment was associated with significantly improved survival compared with placebo in patients with high baseline NTX, whereas survival was comparable between groups in the low-NTX subset. Although the reasons for this are not clear, it is possible that patients with high NTX may have an especially responsive pathophysiology in bone or more likely may have a greater propensity to benefit from early therapy because of their initial higher risk status for potentially life-limiting SREs. This is consistent with the large-scale correlative

report of bone marker levels and outcomes in patients with solid tumors (including NSCLC) published by Brown et al.[12] in which recent bone marker assessments were found to better correlate with risk of SREs and death compared with baseline levels. Moreover, in a recent report in the breast cancer setting, patients with high baseline NTX levels that normalized during zoledronic acid treatment were reported to have longer survival compared with patients whose NTX levels remained persistently elevated.[25] Conversely, patients with normal NTX at baseline are at a lower risk for SREs, and their clinical course and survival prospects are more likely to be driven by extraskeletal disease.

Although the current analyses were exploratory in nature, reduced mortality in zoledronic acid-treated patients versus those who received placebo could be the result of multiple effects that have been reported in previous clinical trials and preclinical assessments. For example, zoledronic acid reduces the risk of potentially life-limiting SREs.[15,16] In phase III clinical trials in which bisphosphonates have reduced the risk of SREs, survival was often longer with bisphosphonate treatment versus placebo, although these differences have seldom reached statistical significance.[26–29] There is also preclinical evidence that zoledronic acid can impede tumor growth, both overall and within the bone microenvironment.[30–36] The relative contributions of each of these effects to the overall survival benefit remains undetermined and may vary based on tumor type and other disease characteristics.

Although the subset of patients with NSCLC who had bone marker assessments was not a randomized cohort in these retrospective analyses, all baseline covariates were included in a complex multivariate model from which the least significant variables were removed in stepwise fashion to achieve a reduced multivariate model. In the overall population of patients with NSCLC who had bone marker assessments, multiple factors correlated with survival. However, among the patients with high NTX levels, only zoledronic acid treatment, requirement for no more than mild analgesics, good performance status, absence of severe lymphopenia, and normal LDH status correlated with improved survival. Of these variables, zoledronic acid treatment compared with placebo was associated with improved survival and constitutes the only factor that can easily be changed by the treating physician.

In the current analyses, survival benefits appeared most profound in patients with factors that were associated with less advanced disease or bone lesions (e.g., shorter cancer duration and elevated NTX that has not reached extremely high levels). Elevated LDH, a known indicator of poor prognosis in NSCLC,[37] was found to be linked not only with reduced survival but with a reduced likelihood of experiencing a survival benefit from zoledronic acid compared with placebo. These findings suggest that zoledronic acid treatment of bone metastases early during the course of disease progression may be the optimum strategy. However, it must be noted that the current indication for zoledronic acid is for the prevention of SREs from bone metastases, and all patients with bone metastases are considered at risk for SREs regardless of their overall disease state or performance status.

Currently, a phase III prospective study is ongoing to evaluate the efficacy of zoledronic acid in delaying or preventing bone metastases in patients with stage III NSCLC. The results of this trial in patients with earlier stages of cancer may underscore the importance of bone-directed therapies even in patients without established bone lesions. The current study has elevated the importance of treating bone metastases in patients with high-risk disease.

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